Attorney's Docket No.: 13691-

002005 / 470-104U\$2CON

:Carlo Brugnara et al: Applicant

Serial No. :10/043,640

:January 10, 2002 Filed

: 2 of 26 Page

Amendments to the Claims:

Listing of Claims:

1-16 (cancelled)

(previously presented) A compound having the structural formula:

$$(R_{5})n \qquad \qquad (R_{5})n \qquad \qquad (R_{5})n \qquad \qquad (R_{5})n \qquad \qquad (R_{7})m \qquad \qquad (R_$$

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

the bond - - - designates a single or double bond;

m is 0, 1, 2, 3 or 4;

each n is independently 0, 1, 2, 3, 4 or 5;

X is C;

Y is absent, (C_1-C_6) alkyl, (C_2-C_6) alkenyl or (C_2-C_6)

alkynyl;

 R_1 is -H, -OR, -SR, -O-C(O)R, -S-C(O)R, -O-C(S)R, -S-

Applicant :Carlo Brugnara et al.
Serial No. :10/043,640
Filed :January 10, 2002
Page : 3 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

C(S)R, or when taken together with R_2 is =0, =\$, =N-OR, a 3-8 membered heterocycloalkyl or a substituted 3-8 membered heterocycloalkyl;

 R_2 is absent or -H;

 R_3 is absent or -H;

with the proviso that R_2 and R_3 are absent at the same time;

 R_4 is -H, -OR', -SR', -N(R')₂, -CN, -NO₂, (C₃-C₈) cycloalkyl, 3-8 membered heterocycloalkyl, -C(0)R', -C(5)R', -C(0)OR', -C(5)OR', -C(5)SR', -C(5)SR', -C(5)N(R')₂;

each R_5 , R_6 and R_7 is independently selected from the group -halogen, $-R^\prime$,

-OR', -SR', $-N(R')_2$, $-ON(R')_2$, $-SN(R')_2$, $-NO_2$, -CN, -C(O)R', -C(S)R', -C(O)OR',

-C(O)SR', -C(S)OR', -CS(S)R', $-C(O)N(R')_2$, $-C(S)N(R')_2$, -C(O)NR'(OR'),

-C(S)NR'(OR'); -C(O)NR'(SR'), -C(S)NR'(SR'), $-CH(CN)_2$, -CH(CO)R']₂,

-CH[C(S)R']₂, -CH[C(O)OR']₂, -CH[C(S)OR']₂, -CH[C(O)SR']₂ and -CH[C(S)SR']₂; with the following provisos:

when - - - is single bond, and X is C, and R_1 is - OH, and R_2 , R_3 and R_4 are H, and Y is absent, then (a) if m is 0, then n is not 0 and at least one of R_5 and R_6 are other than H; (b) if n is 0, then m is not 0 and at least one of R_7 is other than H; or

Serial No. :10/043,640

Filed :January 10, 2002

: 4 of 26 Page

Attorney's Docket No.: 13691-002005 / 470-104US2CON

when -- is single bond, and X is C, and R₁ and R₂ taken together are =0, and Y is absent, and R_3 and R_4 are H, then (a) if m is 0, then n is not 0 and at least one of R_5 and R_6 are other than H; (b) if n is 0, then m is not 0 and at least one of R7 is other than H; or

when - - is single bond, and X is C, and R_1 and R_2 taken together are =0, and Y is absent, and R_3 and R_4 are H, and m = 0, and n = 1 then (a) if R_5 is H, then R_6 is not Br (para), or OMe (para) or OH (para); (b) if R6 is H, then R_5 is not Br (para), or OMe (para) or OH (para); or

when - - is single bond, and X is C, and R_1 , R_2 , R_3 and R_4 are H, and Y is absent, then (a) if m is 0, then n is not 0 and at least one of R5 and R6 is other than H; (b) if n is 0, then m is not 0 and at least one of R7 is other than H; and (c) if m = 0 and n is 1, then R_5 and R_6 are not both -NH2 (para) or -OH (para); or

when - - - is double bond, and X is C, and R_1 and R_4 are H, and R_2 , R_3 and Y are absent, then (a) if m is 0, then n is not 0 and at least one of R_5 and R_6 are other than H; (b) if n is 0, then m is not 0 and at least one of R7 is other than H; (c) if m = 0, and n = 1, then (i) if R_5 is H, then R_6 is not -OMe (para), or Br (para), or -CN (para); (ii) if R_6 is H, then R_5 is not -OMe (para), or Br (para), or -CN (para); or

when - - is single bond, and X is C, and R_1 and R_2 taken together are =0, and Y is CH_2 , and R_3 and R_4 are H,

Attorney's Docket No.: 13691-

002005 / 470-104US2CON

Applicant :Carlo Brugnara et al.

Serial No. :10/043,640

(para); or

Filed :January 10, 2002

: 5 of 26 Page

and m = 0, and n = 1, then R_5 and R_6 are not both -OH

when -- is single bond, and X is C, and R_1 and R_2 taken together are =0, and Y is absent, and R_3 is H, and R_4 is -C(0) OEt, and m = 0, and n = 1, then (a) if R_5 is H, then R_6 is not -OH (para); (b) if R_6 is H, then R_5 is not -OH (para); or

when - - is single bond, and X is C, and R₁ is -OH, and R_2 , R_3 and R_4 are H, and Y is absent, and m = 0, and n = 1, then (a) if R_5 is H, then R_6 is not -Br at the para position; (b) if R₆ is H, then R₅ is not -Br at the para position; or

when -- is single bond, and X is C, and R_1 and R_2 taken together are =N-OR, wherein R = H, and Y is absent, and R_3 , R_4 , R_5 , R_6 and R_7 are H, then the salt is not hydrochloride;

when - - is double bond, and X is C, and R₁ is H, and R_2 , R_3 and Y are absent, and R5, R6 and R7 are H or m and n are both 0 , then R4 is not OR', wherein R' is H;

each R is independently selected from the group -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl and substituted (C₆-C₂₆) alkaryl;

heterocycloalkyl substituents each the are independently selected from the group -CN, -NO₂, -N(R')₂, -OR', $-C(O)N(R')_2$, $-C(S)N(R')_2$, -C(O)OR', -C(S)OR',

Applicant :Carlo Brugnara et al. Serial No. :10/043,640

Filed:January 10, 2002

: 6 of 26 Page

Attorney's Docket No.: 13691-002005 / 470-104US2CON

-C(O)SR', -C(S)SR' and trihalomethyl;

and alkaryl substituents are each the aryl independently selected from the group -halogen, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR',

 $-C(0)N(R')_2$, $-C(S)N(R')_2$ and trihalomethyl;

each R' is independently selected from the group -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl and (C_2-C_6) alkynyl.

The compound of Claim 17, wherein (previously presented) 18. said compound is selected from the group of Compounds 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20.

Applicant

:Carlo Brugnara et al.

Serial No. :10/043,640

Filed

:January 10, 2002

Page

: 7 of 26

Attorney's Docket No.: 13691-

002005 / 470-104US2CON

(18)

(17)

:Carlo Brugnara et al. Applicant

Scrial No. :10/043,640

Filed :January 10, 2002

: 8 of 26 Page

Attorney's Docket No.: 13691-002005 / 470-104U\$2CON

(previously presented) A pharmaceutical composition 19. comprising an effective amount of one or more compounds of formula (I) and a pharmaceutically acceptable excipient, carrier or diluent:

$$(R_8)n$$

$$(R_7)m$$

$$R_1$$

$$R_2$$

$$R_2$$

or a pharmaceutically acceptable salt or hydrates thereof, wherein:

> the bond --- designates a single or double bond; m is 0, 1, 2, 3 or 4; each n is independently 0, 1, 2, 3, 4 or 5; X is C;

Attorney's Docket No.: 13691-002005 / 470-104US2CON

Serial No. :10/043,640

Filed :January 10, 2002 Page : 9 of 26

Y is absent, (C_1-C_6) alkyl, (C_2-C_6) alkenyl or (C_2-C_6) alkynyl;

 R_1 is -H, -OR, -SR, -O-C(O)R, -S-C(O)R, -O-C(S)R, -S-C(S)R, or when taken together with R_z is =0, =S, =N-OR, a 3-8 membered heterocycloalkyl or a substituted 3-8 membered heterocycloalkyl;

 R_2 is absent or -H;

R₃ is absent or -H;

with the proviso that R_2 and R_3 are absent at the same time;

 R_4 is -H, -OR', -SR', -N(R')₂, -CN, -NO₂, (C₃-C₆) cycloalkyl, 3-8 membered heterocycloalkyl, -C(0)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', $-C(0)N(R')_2$ or $-C(S)(NR')_2$;

each R_5 , R_6 and R_7 is independently selected from the group -halogen, -R',

-OR', -SR', $-N(R')_2$, $-ON(R')_2$, $-SN(R')_2$, $-NO_2$, -CN, -C(O)R', -C(\$)R', -C(0)OR',

-C(0)SR', -C(S)OR', -CS(S)R', $-C(O)N(R')_2$, $-C(S)N(R')_2$, -C(0)NR'(OR'),

 $-C(S)NR'(OR'); -C(O)NR'(SR'), -C(S)NR'(SR'), -CH(CN)_2, CH[C(0)R']_{2}$

 $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$ and -CH[C(S)SR']2;

each R is independently selected from the group -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_5-C_{20})

Attorney's Docket No.: 13691-

002005 / 470-104U52CON

Applicant : Carlo Brugnara et al.

Serial No. :10/043,640

:January 10, 2002

: 10 of 26 Page

> aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl substituted (C_6-C_{26}) alkaryl;

> heterocycloalkyl substituents are the independently selected from the group -CN, -NO2, -N(R')2, -OR', $-C(O)N(R')_2$, $-C(S)N(R')_2$, -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR' and trihalomethyl;

> and alkaryl substituents are each the aryl independently selected from the group -halogen, -C(0)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', $-C(0)N(R')_2$, $-C(S)N(R')_2$ and trihalomethyl;

> each R' is independently selected from the group -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl and (C_2-C_6) alkynyl.

(currently amended) A pharmaceutical composition 20. comprising an effective amount of one or more compounds of formula (I) and a pharmaceutically acceptable excipient, carrier or diluent:

$$(R_{5})n$$

$$(R_{7})m$$

$$R_{1}$$

$$R_{2}$$

or a pharmaceutically acceptable salt or hydrates thereof,

Applicant :Carlo Brugnara et al. Serial No. :10/043,640

Filed :January 10, 2002 Page : 11 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

wherein:

the bond --- designates a single or double bond;

m is 0 or 1;

each n is independently 0 or 1;

X is C;

Y is absent, (C_1-C_3) alkyl, (C_2-C_3) alkenyl or (C_2-C_3) alkynyl;

 R_1 is -H, -OR, -O-C(O)R, $-N\Theta_2$ -N(R)₂ or when taken together with R2 is =0,

=N-OR, a 3-5 membered oxirane or 3-5 membered substituted oxirane;

 R_2 is absent or -H;

R₃ is absent or -H;

with the proviso that R_{3} and R_{3} are absent at the same time;

 R_4 is -H, -OR, $-N \otimes_2$ -N(R)₂, -CN, -C(O)OR, -C(O) $N \otimes_2$ N(R)₂ or 5-6 membered dioxoycycloalkyl;

each R₅, R₆ and R₇ is independently selected from the group -R', -F, -Cl or -Br;

each R is independently selected from the group -H, (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_5-C_{10}) aryl, substituted (C_5-C_{10}) aryl, (C_6-C_{13}) alkaryl, substituted (C_6-C_{13}) alkaryl;

the oxirane substituent is -CN, $-NO_2$, $-N(R')_2$, -OR'and trihalomethyl;

> the aryl and alkaryl substituents are

Serial No. :10/043,640

Filed

:January 10, 2002

Page

: 12 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

independently selected from the group -F, -Cl, -Br, -CN, - NO_2 , $-N(R')_2$, -C(O)R', -C(O)OR' and trihalomethyl; R' is -H, (C_1-C_3) alkyl, (C_2-C_3) alkenyl or (C_2-C_3)

alkynyl.

(previously presentd) The pharmaceutical composition of 21. Claim 20, wherein said compound is selected from the group of Compounds 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20.

Applicant

:Carlo Brugnara et al.

Serial No. :10/043,640

Filed

:January 10, 2002 : 13 of 26

Page

Attorney's Docket No.: 13691-

002005 / 470-104U\$2CON

Applicant

:Carlo Brugnara et al.

Serial No. :10/043,640

Filed

:January 10, 2002

Page

: 14 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

(16)(17)(18)and ÒН (19)(20)

22. (previously presented) A method of inhibiting mammalian cell proliferation, said method comprising the step of contacting a mammalian cell in situ with an effective amount of at least one compound having the formula:

Serial No. :10/043,640

Filed :January 10, 2002

Page

: 15 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

$$(R_6)n$$

$$(R_7)m$$

$$R_1$$

$$R_2$$

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

the bond --- designates a single or double bond;

m is 0, 1, 2, 3 or 4;

each n is independently 0, 1, 2, 3, 4 or 5;

X is C;

Y is absent, (C_1-C_6) alkyl, (C_2-C_6) alkenyl or (C_2-C_6) alkynyl;

 R_1 is -H, -OR, -SR, -O-C(O)R, -S-C(O)R, -O-C(S)R, -S-C(S)R, or when taken together with R_2 is =0, =S, =N-OR, a membered heterocycloalkyl or a substituted 3-8 3-8 membered heterocycloalkyl;

 R_2 is absent or -H;

R₃ is absent or -H;

with the proviso that R_2 and R_3 are absent at the same time;

 R_4 is -H, -OR', -SR', -N(R')₂, -CN, -NO₂, (C₃-C₈) cycloalkyl, 3-8 membered heterocycloalkyl, -C(0)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR',

Serial No.:10/043,640

Filed :January 10, 2002

Page :16 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

 $-C(O)N(R')_2$ or $-C(S)N(R')_2$;

each R_5 , R_6 and R_7 is independently selected from the group -halogen, $-R^\prime$,

-OR', -SR', $-N(R')_2$, $-ON(R')_2$, $-SN(R')_2$, $-NO_2$, -CN, -C(O)R', -C(S)R', -C(O)OR',

-C(O)SR', -C(S)OR', -CS(S)R', $-C(O)N(R')_2$, $-C(S)N(R')_2$, -C(O)NR'(OR'),

-C(S)NR'(OR'); -C(O)NR'(SR'), -C(S)NR'(SR'), $-CH(CN)_2,$ $-CH[C(O)R']_2,$

-CH[C(S)R']₂, -CH[C(O)OR']₂, -CH[C(S)OR']₂, -CH[C(O)SR']₂ and -CH[C(S)SR']₂;

each R is independently selected from the group -H, $(C_1-C_6) \ \ alkyl, \ \ (C_2-C_6) \ \ alkenyl, \ \ (C_2-C_6) \ \ alkynyl, \ \ (C_5-C_{20})$ aryl, substituted $(C_5-C_{20}) \ \ aryl, \ \ (C_6-C_{26}) \ \ alkaryl \ \ and$ substituted

 (C_6-C_{26}) alkaryl;

the heterocycloalkyl substituents are each independently selected from the group

-CN, $-NO_2$, $-N(R')_2$, $-C(O)N(R')_2$, $-C(S)N(R')_2$, -C(O)OR', -C(S)OR',

-C(O)SR', -C(S)SR' and trihalomethyl;

the aryl and alkaryl substituents are each independently selected from the group

-halogen, -C(0)R', -C(S)R', -C(0)OR', -C(S)OR', -C(O)SR', -C(S)SR',

 $-C(0)N(R')_2$, $-C(S)N(R')_2$ and trihalomethyl;

each R' is independently selected from the group -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl and (C_2-C_6) alkynyl.

Serial No.:10/043,640

:January 10, 2002 Filed

:17 of 26 Page

Attorney's Docket No.: 13691-002005 / 470-104US2CON

(previously presented) A method of inhibiting mammalian 23. cell proliferation, said method comprising the step of contacting a mammalian cell in situ with an effective amount of at least one compound having the structural formula (I):

$$(R_8)n$$

$$(R_7)m$$

$$R_1$$

$$R_2$$

a pharmaceutically acceptable salt or hydrate thereof, wherein:

the bond --- designates a single or double bond;

m is 0 or 1;

each n is independently 0 or 1;

X is C;

Y is absent, (C_1-C_3) alkyl, (C_2-C_3) alkenyl or (C_2-C_3) alkynyl;

 R_1 is -H, -OR, -O-C(O)R, -N(R)₂, or when taken together with R_2 is =0,

=N-OR, or 3-5 membered oxirane or 3-5 membered substituted oxirane;

R₂ is absent or -H;

 R_3 is absent or -H;

with the proviso that R_2 and R_3 are absent at the same time;

Serial No.:10/043,640

:January 10, 2002 Filed

:18 of 26 Page

Attorney's Docket No.: 13691-002005 / 470-104US2CON

 R_4 is -H, -OR, $-N(R)_2$, -CN, -C(0)OR, -C(0)N(R)₂, or 5-6 membered dioxoycycloalkyl;

each R₅, R₆ and R₇ is independently selected from the group -R', -F, -Cl or -Br;

each R is independently selected from the group -H, (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_5-C_{10}) aryl, substituted (C_5-C_{10}) aryl, (C_6-C_{13}) alkaryl, substituted (C_6-C_{13}) alkaryl;

the oxirane substituent is -CN, -NO₂, -N(R')₂, -OR' and trihalomethyl;

the aryl and alkaryl substituents are each independently selected from the group -F,

-C1, -Br, -CN, $-NO_2$, $-N(R')_2$, -C(O)R', -C(O)OR'trihalomethyl;

R' is -H, (C_1-C_3) alkyl, (C_2-C_3) alkenyl or (C_2-C_3) alkynyl.

24. (previously presented) The method of Claim 23, wherein said compound is selected from the group of Compounds 2, 3, 4, 6, 7, 8, 10, 11, 15, 16, 17, 19 and 20.

Serial No.:10/043,640

Filed :January 10, 2002

Page

:19 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

Serial No.:10/043,640

:January 10, 2002 Filed

Page :20 of 26 Allorney's Docket No.: 13691-002005 / 470-104US2CON

- (previously presented) The method of Claims 22 or 23, 25. wherein said mammalian cell is an endothelial cell, a fibrotic cell or a vascular smooth muscle cell.
- A method of treating a disorder (previously presented) 26. characterized by abnormal cell proliferation, said method comprising the step of administering to a subject in need therapeutically effective amount a pharmaceutical composition according to Claim 19.

Serial No.:10/043,640

Filed :January 10, 2002

Page :21 of 26

Attorney's Docket No.: 13691-002005 / 470 104US2CON

27. (previously presented) A method of treating a disorder characterized by abnormal cell proliferation, said method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to Claim 20, wherein, in the compound of structural formula (I):

$$(R_5)n$$

$$(R_5)n$$

$$(R_7)m$$

$$R_1$$

$$R_2$$

the bond --- designates a single or double bond;

m is 0 or 1;

each n is independently 0 or 1;

X is C;

Y is absent, (C_1-C_3) alkyl, (C_2-C_3) alkenyl or (C_2-C_3) alkynyl;

 $$R_1$$ is -H, -OR,-O-C(O)R, -N(R)2, or when taken together with R_2 is =O,

=N-OR, or a 3-5 membered oxirane or 3-5 membered substituted oxirane;

R₂ is absent or -H;

R₃ is absent or -H;

with the proviso that R_2 and R_3 are absent at the same time;

Serial No.:10/043,640

Filed :January 10, 2002

:22 of 26 Page

Attorney's Docket No.: 13691-002005 / 470-104US2CON

 R_4 is -H, -OR, -N(R)₂, -CN, -C(O)OR, -C(O)N(R)₂ or 5-6 membered dioxoycycloalkyl;

each R_5 , R_6 and R_7 is independently selected from the group -R', -F, -Cl or -Br;

each R is independently selected from the group -H, (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, (C_5-C_{10}) substituted (C_5-C_{10}) aryl, (C_6-C_{13}) alkaryl, aryl, substituted

 (C_6-C_{13}) alkaryl;

the oxirane substituent is -CN, -NO₂, -N(R')₂, -OR' and trihalomethyl:

the aryl and alkaryl substituents are independently selected from the group -F,

-Cl, -Br, -CN, -NO₂, -N(R')₂, -C(O)R', -C(O)OR' a'nd trihalomethyl;

R' is -H, (C_1-C_3) alkyl, (C_2-C_3) alkenyl or (C_2-C_3) alkynyl.

(previously presented) The method of Claim 26, wherein said compound is selected from the group of Compounds 2, 3, 4, 6, 7, 8, 10, 11, 15, 16, 17, 19 and 20.

Serial No.:10/043,640

Filed :January 10, 2002

Page :23 of 26

Attorney's Docket No.: 13691-

002005 / 470·104US2CON

(6)

Serial No.:10/043,640

Filed :January 10, 2002 Page :24 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

- 29. (previously presented) The method of Claims 26 or 27, wherein said disorder characterized by abnormal cell proliferation is cancer, a blood vessel proliferative disorder, a fibrotic disorder or an arteriosclerotic condition.
- 30. (previously presented) The method of Claim 29, wherein

Serial No.:10/043,640

Filed :January 10, 2002

Page :25 of 26

Attorney's Docket No.: 13691-002005 / 470-104US2CON

said step of administering is per oral, parenteral or intravenous.

- 31. (previously presented) The method of Claims 26 or 27, wherein said disorder characterized by abnormal cell proliferation is a dermatological disease or Kaposi's sarcoma and said administration is transdermal.
- 32. (previously presented) The method of Claim 31, wherein said dermatological disease is selected from the group keloids, hypertonic scars, seborrheic dermatosis, papilloma virus infection, eczema and actinic keratosis.